Definitive-intent radiotherapy for sinonasal carcinoma in cats: a multicenter retrospective assessment

Stiborova, Katerina ; Meier, Valeria Sabina ; Takada, Marilia ; Turek, Michelle ; Poirier, Valerie J ; Laliberte, Sarah ; Rohrer Bley, Carla

Abstract: Treatment of epithelial sinonasal tumors in cats is not commonly reported. Palliative radiation protocols have been described more often than definitive-intent protocols. In this multi-institutional retrospective study, we included 27 cats treated with single-modality radiotherapy. Cats were irradiated using 10 daily fractions of 4.2Gy. Three cats (11.1%) experienced a complete clinical response and 17 (63%) had a partial clinical response. Stable clinical disease was noted in three cats (11.1%). Four cats (14.8%) showed progression within 3 months following treatment. The median time to progression for all cases was 269 days (95% CI: 225;314). The proportion of cats free of progression at 1 and 2 years was 24% (95%CI: 22%;26%) and 5% (95%CI: 5%;6%), respectively. None of the prognostic factors evaluated were predictive of outcome (anemia, tumor volume at the time of staging, modified Adams stage, intracranial involvement, facial deformity, epistaxis, inappetence or weight loss). Median overall survival (OS) for all deaths was 452 days (95%CI: 334;571). The proportion of cats alive at 1 and 2 years was 57% (95%CI: 37%;77%) and 27% (95%CI: 25%;29%), respectively. Surprisingly, cats with epistaxis had a longer median OS of 828 days (95%CI: 356;1301) compared to 296 days (95%CI: 85;508) in cats without epistaxis, (p=0.04, Breslow). Radiation therapy used as a single modality for the treatment of feline sinonasal carcinoma improved clinical signs and was well tolerated.

DOI: https://doi.org/10.1111/vco.12583

Definitive-intent radiotherapy for sinonasal carcinoma in cats: a multicenter retrospective assessment

Katerina Stiborova[1], Valeria Meier[1,2], Marilia Takada[3], Michelle Turek[3], Valerie J. Poirier[4], Sarah Laliberte[4], Carla Rohrer Bley[1]

[1]Division of Radiation Oncology, Small Animal Department, Vetsuisse Faculty, University of Zurich, 8057 Zurich, Switzerland

[2]Department of Physics, University of Zurich, Zurich, Switzerland

[3]Department of Surgical Sciences, School of Veterinary Medicine, University of Wisconsin-Madison, Madison, Wisconsin, USA

[4]Animal Cancer Centre, Ontario Veterinary College, University of Guelph, Guelph, Ontario, Canada

Short Title: Radiation therapy for sinonasal carcinoma in cats

Corresponding Author:

Katerina Stiborova, Division of Radiation Oncology, Vetsuisse Faculty, University of Zurich, Winterthurerstrasse 260, CH-8057 Zurich, Switzerland

stiborovak@gmail.com

Keywords: adenocarcinoma, cancer, feline, IMRT, nasal

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/vco.12583

Conflict of interest declaration:

The authors have no conflict of interest to report.

Abstract

Treatment of epithelial sinonasal tumors in cats is not commonly reported. In the newer reports palliative radiation protocols have been described more often than definitive-intent protocols. In this multi-institutional retrospective study, we included 27 cats treated with single-modality radiotherapy. Cats were irradiated using 10 daily fractions of 4.2Gy. Three cats (11.1%) experienced a complete clinical response and 17 (63%) had a partial clinical response. Stable clinical disease was noted in three cats (11.1%). Four cats (14.8%) showed progression within 3 months following treatment. The median time to progression for all cases was 269 days (95% CI: 225;314). The proportion of cats free of progression at 1 and 2 years was 24% (95%CI: 22%;26%) and 5% (95%CI: 5%;6%), respectively. None of the prognostic factors evaluated were predictive of outcome (anemia, tumor volume at the time of staging, modified Adams stage, intracranial involvement, facial deformity, epistaxis, inappetence or weight loss). Median overall survival (OS) for all deaths was 452 days (95%CI: 334;571). The proportion of cats alive at 1 and 2 years was 57% (95%CI: 37%;77%)

and 27% (95%CI: 25%;29%), respectively. Surprisingly, cats with epistaxis had a longer median OS of 828 days (95%CI: 356;1301) compared to 296 days (95%CI: 85;508) in cats without epistaxis, (p=.04, Breslow). Radiation therapy used as a single modality for the treatment of feline sinonasal carcinoma improved clinical signs and was well tolerated but progression within a year was common.

Introduction

Sinonasal neoplasms represent 1-8.4% of all tumors in cats and about 90% are malignant.(1, 2) Nearly half of sinonasal tumors in cats are of epithelial origin.(3, 4) Treatments such as surgery(1, 5), combination surgery and radiation therapy(1), and radiation therapy alone(6, 7) are described. Chemotherapy as a single modality is not commonly reported in cats with epithelial neoplasms of sinonasal origin. Carboplatin was used for chemoembolization after postoperative tumor recurrence in one patient that survived for over 800 days.(8) Radiation therapy on gross disease or after surgery is treatment of choice in head and neck tumors in human patients.(9)

Treatment of epithelial sinonasal tumors in cats is not well established and in the newer reports palliative radiation protocols are described more often than definitive-intent protocols.(3, 7, 10, 11)While radiation therapy seems to be the best option due to the complex anatomy of the cat's nasal passages (wide surgical margins impossible), it is unclear if patients would benefit from a more dose- or schedule-intensive protocol.(12) While some studies(1, 3, 13) in the past reported outcome data of different nasal tumor histologies together, nasal epithelial tumors most likely have an inferior prognosis compared to lymphomas.(7, 10, 12, 14) It is unclear if the outcome of epithelial tumors can be improved, even if a more intensive protocol is used. In the dog, radiation therapy for sinonasal tumors is standard of care and the long-established definitive-intent protocol of 10x4.2Gy is still often used.(15-17)

Two previous retrospective studies(3, 10) described radiation therapy for epithelial sinonasal neoplasms using palliative protocols and two investigated non-lymphoproliferative neoplasms of the nasal cavity treated with definitive-intent protocols.(7, 11) Median overall survival was described as favorable, varying between 11.5-14.4 months, however confidence

intervals were not reported.(3, 7, 10) Prognosis was negatively impacted in cats that had a loss of appetite at the time of therapy and purebred cats seemed to fare better.(3)

Studies evaluating a standardized radiation treatment protocol in cats with epithelial sinonasal tumors are lacking, likely in part as a result of the relative rarity of these tumors. The median survival times above were similar between the different studies regardless of treatment intent (palliation vs. definitive intent). However, there was a large disparity in the outcome, survival times were varying between 21-2391 days in one study(3), and between 153-477 days(10) and 30-1080 days(7) in two other studies. This disparity could have several causes: the lack of standardization in tumor type (epithelial and non-epithelial tumors are described together); different treatment approaches including varying radiation prescriptions and protocols (2-6 fractions of 4-8.1Gy per fraction(3, 10), with total dose 16-36Gy(3, 10) or 12x 4Gy(7, 11)); and different irradiation techniques, or due to natural variation in tumor biology. Furthermore, due to the relative rarity of this tumor type, only small numbers of cats with epithelial tumors were treated.

In this multicenter retrospective study, we collected information about cats with epithelial sinonasal tumors treated with a 10x4.2Gy single-modality radiation protocol. We describe the outcome after definitive-intent radiation therapy and investigate the influence of potential prognostic variables.

Material and methods:

Patient Characteristics and Tumor Staging

Medical records of cats diagnosed with a sinonasal epithelial neoplasm were retrospectively reviewed. All cats treated since starting the definitive-intent protocol of 10x4.2Gy were included in the study. Cases from three institutions were included: X, X, X. Inclusion criteria were a cytological or histopathological diagnosis of an epithelial neoplasm of the sinonasal

cavity, nasopharynx, or both (based on the original reports, none of the samples were reviewed); tumor staging including computed tomography (CT) of the head; thoracic imaging both reported by board certified radiologists; treatment with definitive-intent radiotherapy using 10x4.2Gy delivered daily Monday to Friday with no adjuvant chemotherapy or surgery; availability of treatment planning details; follow up of at least 3 months after radiation unless death occurred earlier. Cytological evaluation of the mandibular and medial retropharyngeal lymph nodes was at the discretion of the clinician and not mandatory for inclusion. Cats were excluded if they had distant metastasis at diagnosis or received prior treatment with radiation therapy, chemotherapy or surgery.

Participating contributors were provided a data collection form for each case. The following information was retrieved from the medical records: signalment (breed, age, sex, weight), clinical signs before the start of treatment (yes or no: nasal discharge, epistaxis, sneezing, facial deformity, stertor, inappetence and weight loss), tumor location (unilateral or bilateral nasal cavity, nasopharynx), presence (yes, no) and location of lymph node metastasis; pre-treatment complete blood count and serum biochemistry (yes, no); pre-radiotherapy hematocrit; co-morbidities. Tumors were classified according to the canine modified Adams tumor staging system(18) by the participating contributors as follows: stage 1 (tumor confined to one nasal passage, paranasal sinus, or frontal sinus, no bone involvement beyond turbinates), stage 2 (any bone involvement, but no evidence of orbital or subcutaneous or submucosal mass), stage 3 (orbital, nasopharyngeal, subcutaneous or submucosal involvement), stage 4 (tumor causing lysis of the cribriform plate). Stage 4 tumors were sub-classified into those with and without intracranial extension beyond the cribriform plate. If the histopathology report was available tumor type was recorded. Results of the complete blood count including hematocrit and abnormal biochemistry results were recorded. Anemia was defined as hematocrit below the institution's own laboratory reference range.

Radiation Information

Information collected about radiation therapy included date of start and end of therapy, radiation delivery and treatment planning systems, irradiation of regional lymph nodes (yes, no), patient immobilization and position verification procedures. The gross tumor volume (GTV), clinical target volume (CTV) and planning target volume (PTV) were recorded. Target and organ at risk (19) contouring practices were not standardized. GTV was contoured on CT scan (all institutions). CTV expansion was 1cm within the nasal cavity, often including bone and soft tissue if tumor was extending outside of the nasal cavity (Institution X and X) and CTV represented 2cm expansion rostral/caudal to GTV within the nasal cavity/nasopharynx considering normal tissue planes (Institution X). PTV represented a 2mm expansion isotropic (common for all institutions). Dose statistics for targets and OAR were not recorded.

Follow-up and Response Assessment

Follow up information gathered from the medical records came from recheck examination notes at the treatment institutions or from phone calls to referring veterinarians or cat owners. Complete clinical response to treatment was defined as resolution of previously reported clinical signs. Partial clinical response was defined as improvement of the previously reported clinical signs. When follow up CT was available, tumor response was recorded by the contributing participant as a complete response, partial response, stable disease or progressive disease based on diagnostic imaging reports in the medical record. Objective tumor response criteria were not standardized. When the clinical response conflicted with the imaging response, the least favorable response trumped the more favorable one (clinical complete response + partial imaging response = partial response). Cats were assessed to have stable disease if no clinical improvement or deterioration was noticed on rechecks or

imaging. Progressive disease was defined as either recurrence of clinical nasal signs that were refractory to antibiotics, tumor progression on imaging or development of local or distant metastasis.

Progressive disease was described in terms of time to progression after radiation, location of progression, clinical signs at progression, and diagnostic work-up and additional therapy. Progression was defined as "local" if relapse occurred at the original tumor site (sinonasal cavity and/or nasopharynx and/or regional lymph nodes), or "systemic" if distant metastasis was documented. Progressive disease was considered "confirmed" if cytological or histopathological confirmation of carcinoma at progression was available or if recurrence of a mass at the original location of the tumor was detected by CT. Progressive disease was considered "suspected" when there was recurrence of clinical nasal signs that were not responsive to systemic treatment such as antibiotics.

Cats with resolution of nasal signs to antibiotic therapy after radiation were considered to have chronic rhinitis as a possible late effect of radiation therapy.

Radiation toxicity was defined as early effects if occurring < 3 months after radiotherapy and late effects if occurring ≥3 months. Grading of radiation adverse effects was done retrospectively from the medical records using the Veterinary Radiation Therapy Oncology Group (VRTOG) toxicity criteria.(20)

Statistical analysis

Data were coded in Microsoft Excel and analyzed with SPSS (IBM® SPSS® Statistics, Version 25). Data were used as submitted in an excel table by the participating contributors. Description of quantitative data characteristics, other than time to progression (TTP) and overall survival is given by mean (± SD), unless otherwise specified. Description of

qualitative characteristics is provided in absolute and relative frequencies. A graphical assessment and Shapiro-Wilk normality test were performed on all data. TTP was defined as the interval between the first day of radiation therapy to confirmed (diagnostic imaging and/or cytology) or clinically suspected progression of disease (local, systemic). Cats free of progression at the time of data analysis or death or that were lost to follow-up were censored for TTP analysis at the date of death, the last hospital visit or last contact by phone with the owner or veterinarian. OS was defined as the interval between the first fraction of radiation and death. For OS, all deaths were considered events and cats still alive at the time of data analysis or lost to follow-up were censored at the last date known to be alive. For the follow-up time estimate, cats were censored at the time of death. OS and TTP were coded and analyzed with Kaplan-Meier survival analysis accompanied by the log-rank or Breslow-Gehan-Wilcoxon tests. In the absence of crossing of survival curves, the log-rank test was applied. Otherwise the Breslow-Gehan-Wilcoxon test was used. The univariate and multiple Cox-regression analysis was used to determine whether the following factors were significantly associated with TTP or OS: sex, age, weight, anemia, facial deformity, epistaxis, inappetence, weight loss, GTV, PTV, CTV, modified Adams tumor stage, intracranial involvement, tumor location, locoregional lymph nodes metastases, treatment institution. Median TTP and median OS are reported with the corresponding 95% confidence intervals (95%CI). Results of statistical analyses with p-value <0.05 were considered statistically significant.

Results

Twenty-seven cats diagnosed with an epithelial sinonasal tumor were treated with 10x4.2Gy between 2014 and 2018. None of the cats were excluded. Eleven cats were from the X, 10 cats from the X and six from X. Eleven were spayed females and 16 were neutered males.

The most common breed was domestic shorthair (n=25), and two cats were Siamese. Age ranged from 6.1-18 years with a mean of 12.7 (± 3.2) years and weight ranged from 2.5-11.8 kg with a mean of 4.8 (± 1.9) kg. Four of the 27 cats (14.8%) were anemic at the time of diagnosis [median hematocrit 39% (IQR: 11.0)]. The most commonly presenting sign was nasal discharge in 19 cats (70.4%), 12 (44.4%) of which also had epistaxis. Sneezing was present in 16 cats (59.3%), stertor in 12 (44.4%), and 11 cats (40.7%) had a facial deformity. Inappetence and weight loss were recorded in six (22.2%) and three (11.1%) cats, respectively. Five cats (18.5%) had unilateral nasal disease without nasopharyngeal involvement and four (14.8%) had unilateral disease with nasopharyngeal involvement. Bilateral presence of the tumor with or without nasopharyngeal disease was seen in eight (29.8%) and seven (25.9%) cats, respectively. Tumor was confined to the nasopharynx in three (11.1%) cats. When we grouped the extent of disease according to the modified Adam's staging method for nasal tumors in dogs, four tumors (14.8%) were stage 1, one tumor (3.7%) was stage 2, eight tumors (29.6%) were stage 3, and 14 tumors (51.9%) were stage 4. Seven of the cats with stage 4 tumors (25.9% of all cats) had intracranial extension beyond the cribriform plate. The diagnosis was confirmed by histology in all but one cat. The latter was diagnosed cytologically as a carcinoma. The histological reports revealed 19 (73.1%) adenocarcinomas, four (15.3%) tubular carcinomas, two (7.7%) undifferentiated carcinomas and one (3.8%) squamous cell carcinoma. Immunohistochemistry was not performed. Bilateral mandibular lymph nodes were evaluated cytologically in all 27 cats, and retropharyngeal lymph node cytology was available for six cats. Two cats had confirmed lymph node metastasis: one in the ipsilateral mandibular lymph node and one in the ipsilateral mandibular and prescapular lymph node. In the latter, the diagnosis of metastasis was suspected, but not confirmed. The diagnostic and tumor staging work-up included hematology, serum biochemistry, and thoracic imaging (radiographs or CT) in all cats.

Radiation Planning and Treatment

Computed tomography for treatment planning was performed with either a Brilliance 16-slice [Philips Health Care Ltd, Best, Netherlands (cases from X], a LightSpeed 3.X 8-slice [GE Medical Systems, Milwaukee, WI, USA (cases from X)] or a BrightSpeed 16-slice [GE Healthcare, Milwaukee, WI, USA (cases from X)] CT. The thickness of the slices varied between 1.5-2mm. Computed tomography scans of the area of interest were obtained before and after intravenous administration of a bolus of contrast medium. The post-contrast images were co-registered with the native planning CT images for better delineation. Mean GTV was 10.5 cm^3 (± 9.2). Mean CTV was 21.6 cm^3 (± 13.2). Mean PTV was 34.6 cm^3 (± 18.7).

All cats were treated with 10 daily fractions of 4.2Gy using 6 MV x-rays. Twenty-four cats (88.9%) were treated with intensity-modulated radiotherapy (IMRT) and 3 (11.1%) with 3D conformal radiotherapy (3DCRT) using beam modifying wedges and an 80 or 120 multi-leaf collimator (Clinac iX, Varian, Palo Alto, USA; cases from X, and X respectively). IMRT was delivered using dynamic IMRT (Clinac iX, Varian, Palo Alto, USA; cases from X, X in 14 cats and helical tomotherapy (TomoTherapy HiArt Treatment System®, Accuray Inc., Sunnyvale, CA, USA; cases from X in 10 cats. In thirteen patients a bolus was placed on the cats' heads in order to create sufficient dose build-up and reduce the depth of the maximal dose (D_{max}). This consisted either of a Superflab® made of synthetic oil gel (7 cases from X) or a custom-made water equivalent bolus made of gauze and vaseline (6 cases from X).

Image-guidance was performed using daily kilovolt (kV)-kV orthogonal radiographs (n=4, cats from X), kV-cone-beam CT (CBCT) once to three times during the treatment course (n=5, cats from X), kV-cone-beam CT (CBCT) twice a week for a total of 4 CBCT (n=2, cats from X), daily helical MV-CT (n=10 cats from X), and daily kV-CBCT (n=6, cats from X).

At all institutions, cats were under general anesthesia and immobilized for both the planning

CT and daily treatment using a customized bite block and vacuum mattress. For dynamic IMRT and 3DCRT treatment planning, the Eclipse™ Treatment Planning system (version 10.0, 11.5.0 or 15.1, Varian Oncology Systems, Palo Alto, California) was used with the AAA photon dose calculation model with heterogeneity correction. Tomotherapy plans were created using the convolution superposition algorithm, including heterogeneity correction (Tomotherapy Planning Station Hi-Art versions 3 to 5). The planning aim for all cats was to deliver dose to the PTV such that 95% of the PTV received between 95-107% of the prescribed dose. However, due to the retrospective nature of the study there was no information on how many of the plans adhered to those aims. Maximum, mean and minimum dose is reported in Table 1.

Dosimetric quality assurance was performed by a medical physicist for all IMRT treatment plans delivered at all institutions and considered within tolerance. Median overall treatment time was 12 days (range 12-18 days; IQR: 2.0). The treatment delay was due to breaks over the weekend(s) and bank holidays. The locoregional lymph nodes, including bilateral mandibular and bilateral medial retropharyngeal nodes, were prophylactically irradiated using the same treatment plan in four of the 27 cats (14.8%). Two cats (7.4%) with (suspected) locoregional metastasis received radiation of the affected lymph nodes using the same treatment plan. The others 21 cats (77.8%) received no irradiation of the locoregional lymph nodes. Cats were prescribed supportive medications including steroids, non-steroidal anti-inflammatory drugs (NSAID) and/or antibiotics as needed to manage early radiation toxicity.

Radiation Toxicity, Follow-up and Outcome

Follow-up was not standardized. Toxicities were graded during the regular follow-up visits. Data regarding toxicities were extracted from the clinical records (grade and/or photograph).

Early radiation toxicity was assessed in all cats between 1-3 weeks after the end of radiation therapy. Twelve (44.4%) cats exhibited no side effects and 15 cats (55.6%) developed mild to moderate radiation toxicity: mild grade 1 skin reactions were observed in 12 cats (44.4%), grade 1 mucosal reactions in three cats (11.1%), grade 1 ocular reactions in two cats (7.4%), moderate grade 2 ocular and mucosal reactions in one cat (3.7%), and moderate grade 3 mucosal reaction in one cat (3.7%). All but four cats were assessed for late radiation toxicity. The recommended re-check schedule for assessment of late toxicity was every 3 months until 12 months post RT and then every 6 months or every 3 months until 24 months post RT but this varied between the different institutions and cats. Nine cats (33.3%) developed late side effects: mild, grade 1 skin reactions (leukotrichia, alopecia) were seen in eight cats (29.6%), grade 1 ocular reactions in five cats (18.5%) and moderate grade 2 ocular reactions in one cat (3.7%). Eleven of 27 (40.7%) cats showed signs of intermittent or chronic rhinitis. Central nervous system or bone toxicity were not reported. Three cats treated with 3DCRT displayed similar side effects as cats treated with IMRT. One developed early (skin) and one late (eye) side effects, both VRTOG grade 1.

Clinical response to radiation was evaluated in all 27 cats. Three cats (11.1%) experienced a complete clinical response and 17 (63%) had a partial clinical response. Stable clinical signs were noted in three cats (11.1%). Four cats (14.8%) had a rapid worsening of clinical signs within the first three months after radiation therapy and were considered progressive without notable improvement. Objective tumor response based on imaging was difficult to assess, as there were no standardized time points. The motivation to perform a post-treatment CT scan was mainly if progression was suspected based on the clinical examination. Follow-up CT was performed between 3 and 18 months after radiotherapy in 17/27 cats. Four of these 17 cats had a partial response, six had stable disease and seven had progressive disease.

The mean follow-up time for all cats was 987 days, (95% CI: 756;1215, range 119-1262). During this time, a total of 23 cats (85.2%) developed suspected local progressive disease. In two cats (7.4%), previously free of metastases, disease progression to the regional lymph was cytologically confirmed. The latter disease progression was cytologically confirmed. None of the cats had documented systemic progression.

The median TTP for all cases was 269 days (95% CI: 225;314). The proportion of cats free of progression at 1 and 2 years was 24% (95%CI: 22%;26%) and 5% (95%CI: 5%;6%), respectively (Figure 1). We found no significant difference in TTP between the 3 institutions: median TTP for 11 cats treated at the X was 225 days (95%CI: 111;340, range 75-1262), median TTP for 10 cats treated at the X was 168 days (95%CI: 26;311, range 52-521), and median TTP for 6 cats treated at the X was 296 days (95%CI: 204;314, range 247-389), (p=.06, log-rank). None of the factors including anemia (p=.20, log-rank), tumor size (GTV) at time of staging (p=.95, log-rank), modified Adams stage (p=.10, log-rank), intracranial involvement (p=.10, log-rank), facial deformity (p=.95, log-rank), epistaxis (p=.15, log-rank), inappetence (p=.06, log-rank) or weight loss (p=.74, log-rank) were predictive of TTP.

Three cats were re-irradiated after developing progressive disease: all of them received an additional five daily fractions of 4Gy 281, 389, and 521 days after the first treatment. An additional six cats received adjuvant chemotherapy at progression: toceranib was prescribed to four cats, and carboplatin and doxorubicin were used in one cat each. Twelve cats received NSAIDs and/or antibiotics for supportive treatment of progressive clinical signs.

Information regarding outcomes relied on consultation in the radiation facility or with the private veterinarian in 17 cases and on telephone follow-up with the owners in the remaining 10 cases. Median OS for all deaths was 452 days (95%CI: 334;571) (Figure 2). We found no significant difference in OS between the 3 institutions: median OS for 11 cats treated at the X was 452 days (95%CI: 350;555, range 153-1262), median OS for 10 cats treated at the X was

575 days (95%CI: 0;1365, range 67-829), and median OS for 6 cats treated at the X was 396 days (95%CI: 241;552, range 256-515), (p=.780, log-rank).

The proportion of cats alive at 1 and 2 years was 57% (95%CI: 37%;77%) and 27% (95%CI: 25%;29%), respectively. Cats with epistaxis lived significantly longer, with a median OS of 828 days (95%CI: 356;1301) vs. 296 days (95%CI: 85;508) in cats without epistaxis, (p=.04, Breslow) (Figure 3). None of the other factors were predictive of OS. The TTP and survival of the two cats with initial locoregional metastases were 225, respectively 355 days, and 452, respectively 362 days.

Twenty-one animals (77.8%) died. Fifteen (55.6%) deaths were tumor-related and 5 (18.5%) were tumor-unrelated (car accident, high grade intestinal lymphoma, chronic kidney disease). Cause of death was not known in 1 cat (3.7%). In all cats with tumor-related death, the cause was local progression and progressive clinical signs. All cast died without known systemic metastasis or without clinical signs related to systemic metastasis.

Discussion

As all cats in our study were staged with CT, we assessed the extent of disease using the modified canine Adams staging system.(18) Local tumor extent has not been shown to be predictive of outcome in cats with nasal tumors in previous studies(7), and was not associated with TTP or OS in this study either. Similarly, tumor extension into the calvarium, which affected 25% of cats in this study, was not a prognostic indicator. Consistent with previous studies(18, 21), most cats in this cohort presented with advanced stage disease classified as stage 3 or 4 according to the modified Adams system. It is unclear why cats are presented in rather advanced disease stages. It is possible that cats with nasal tumors are misdiagnosed as having chronic rhinitis, the second most common cause of nasal disease in cats(22), and that work up including advanced imaging and other diagnostics is delayed while cats are treated

symptomatically with steroids, NSAIDs and/or antibiotics.(21-23) Cats in previous studies seemed to show only mild signs with stage 4 disease, despite having measurable intracranial tumor extension.(3, 7, 10) Stage 4 disease is a negative prognostic factor in dogs with nasal tumors, reducing overall survival time.(18, 24, 25) In cats, however, we found no influence of stage on outcome based on the modified Adams system. Similarly, most of the other variables we evaluated, including anemia at time of staging, tumor size, facial deformity, inappetence or weight loss were not predictive of TTP or OS. The only prognostic variable was epistaxis, which correlated with longer OS. This is contrary to dogs with nasal carcinoma, where epistaxis is associated with a 2.3 fold increased risk of dying.(26)

The side effect profile observed in this cohort of cats treated with conformal radiation delivery techniques (IMRT in 24/27) was favorable. The majority of side effects were mild (grade 1) or moderate (grade 2). Toxicity profiles would be expected to be different with less-conformal radiation delivery systems. Overall, this study suggests that the protocol described herein is safe and well-tolerated when IMRT is used and can be recommended for the treatment of sinonasal carcinoma in cats. However, since dose statistics for organs at risk were not recorded it is not possible to correlate toxicity and radiation dose.

After definitive-intent radiation therapy using 10x4.2Gy, we found local tumor progression or progression of nasal signs in the majority of cats (85.2%). Median TTP was short at 9 months, with 76% of cats showing progression at 1 year. This high rate of local treatment failure was also found by other colleagues, where 79.8% of the cats (epithelial or mesenchymal tumors)(7) and 61.3% of the cats (epithelial tumors or localized lymphoma)(3) progressed locally at one year. However, most studies, including ours, are limited by a lack of standardized follow-up imaging to assess tumor status. It is unclear to what extent our assessment of progressive disease based on nasal signs being unresponsive to antibiotics represents true tumor progression. Similarly, tumor response to radiation was difficult to

objectively evaluate and was assessed based on resolution of nasal signs. A prospective study with regular, standardized follow up imaging is necessary to accurately estimate TTP.

Clinical signs improved after radiation therapy in most cats in this study (74%). Three cats experienced complete resolution of clinical signs and 17 had partial resolution or improvement of signs. It is notable, however, that four cats experienced rapid worsening of clinical signs within 3 months after radiation, without improvement.

In the present study, the OS was approximately half a year longer than the TTP, which could be associated with the response of some cats to the rescue protocols instituted at disease progression (chemotherapy, palliative radiotherapy), and/or to slow progression of disease and the level of tolerance of cats to the clinical signs. The median OS was 15 months (95%CI: 11.1-19.0). Interestingly, previous radiation studies describing more palliative approaches have reported median OS times of 15 months (95%CI: 6.8-23.8)(3) and 12.6 months(10), confidence interval was not available for the latter study. Notwithstanding, the disparity in reported outcomes in the literature is wide. This could be due to differences in the tumors themselves (biological factors), treatment-related factors (effectiveness of RT delivery, treatment planning and delivery) or to limitations of study design (small case numbers, different tumor types described together, disparity of the treatment protocol within the study). It is not clear if there is truly disparity in outcome among cats with epithelial sinonasal tumors or if the variation in reported outcomes is the result of study bias. Future studies should aim to determine the role, if any, for more intensive protocols such as the one described here versus that of more palliative radiation approaches.

We acknowledge the limitations inherent with retrospective and multicenter studies. Tumor staging, treatment planning and delivery, as well as follow-up procedures were not standardized. Importantly, the difficulty in objectively assessing tumor progression without standardized follow-up imaging can under- or overestimate tumor response and progression.

Furthermore, although the three institutions used the same radiation therapy protocol, the quality of treatment plans with respect to tumor dose coverage and OAR exposure was not evaluated. Dose distribution is critical to radiation effectiveness, as well as to toxicity, and underdosage of the tumor can contribute to treatment failure. In the head and neck area of cats, the absorbed dose to PTV can be lower than intended or recommended, most likely due to shortcomings of adequate bolus placement or due to air soft tissue interfaces such as in the frontal sinus or oral cavity.(12, 17, 27) Such underdosage can contribute to treatment failure even in the face of a protocol with sufficiently high anti-tumor dose. Underdosages due to lack of bolus can be prevented by placement of bolus material on the cats' head. Adherence to recommended dose distribution guidelines and accurate reporting of dose delivered to tumor and OAR should be a focus of future prospective studies.

Conclusion

Radiation therapy used as a single modality for the treatment of sinonasal carcinoma in cats improved clinical signs and resulted in a median survival time of 15 months in a cohort of 27 cats treated with 10x4.2Gy. Using conformal delivery systems, the treatment was well tolerated, but progression of nasal signs occurred within 9 months in the majority of cats.

Data accessibility

The data that support the findings of this study are available from the corresponding author upon reasonable request

1. Cox NR, Brawner WR, Powers RD, Wright JC. Tumors of the Nose and Paranasal Sinuses in Cats - 32 Cases with Comparison to a National Database (1977 through 1987). Journal of the American Animal Hospital Association. 1991;27(3):339-47. PubMed PMID: WOS:A1991FM20200016.

2. Moulton JE. Tumors of respiratory tract. In: Moulton JE, editor. Tumors in Domestic Animals. 1. Berkeley, CA: University of California Press; 1990. p. 308-13.
3. Fujiwara-Igarashi A, Fujimori T, Oka M, Nishimura Y, Hamamoto Y, Kazato Y, et al. Evaluation of outcomes and radiation complications in 65 cats with nasal tumours treated with palliative hypofractionated radiotherapy. Vet J. 2014;202(3):455-61. doi: 10.1016/j.tvjl.2014.09.016. PubMed PMID: WOS:000348017500010.
4. Mukaratirwa S, Hove T, Esmann JB, Hoj CJ, Permin A, Nansen P. A survey of parasitic nematode infections of chickens in rural Zimbabwe. Onderstepoort J Vet Res. 2001;68(3):183-6. Epub 2002/01/05. PubMed PMID: 11769349.
5. Legendre AM, Carrig CB, Howard DR, Dade AW. Nasal tumor in a cat. J Am Vet Med Assoc. 1975;167(6):481-3. Epub 1975/09/15. PubMed PMID: 1174355.
6. Lord PF, Kapp DS, Schwartz A, Morrow DT. Osteogenic-Sarcoma of the Nasal Cavity in a Cat - Postoperative Control with High Dose-Per-Fraction Radiation-Therapy and Metronidazole. Vet Radiology. 1982;23(1):23-6. doi: DOI 10.1111/j.1740-8261.1982.tb00704.x. PubMed PMID: WOS:A1982NE81100005.
7. Theon AP, Peaston AE, Madewell BR, Dungworth DL. Irradiation of Nonlymphoproliferative Neoplasms of the Nasal Cavity and Paranasal Sinuses in 16 Cats. Journal of the American Veterinary Medical Association. 1994;204(1):78-83. PubMed PMID: WOS:A1994MN97800019.
8. Henry KM, Schwarz T, Weisse C, Muravnick KB. Cystic nasal adenocarcinoma in a cat treated with piroxicam and chemoembolization. Journal of the American Animal Hospital Association. 2007;43(6):347-51. PubMed PMID: WOS:000250617200007.
9. Lydiatt WM, Patel SG, O'Sullivan B, Brandwein MS, Ridge JA, Migliacci JC, et al. Head and Neck cancers-major changes in the American Joint Committee on cancer eighth edition cancer staging manual. CA Cancer J Clin. 2017;67(2):122-37. Epub 2017/01/28. doi: 10.3322/caac.21389. PubMed PMID: 28128848.
10. Mellanby RJ, Herrtage ME, Dobson JM. Long-term outcome of eight cats with non-lymphoproliferative nasal tumours treated by megavoltage radiotherapy. J Feline Med Surg. 2002;4(2):77-81. Epub 2002/05/25. doi: 10.1053/jfms.2001.0159. PubMed PMID: 12027506.
11. Straw RC, Withrow SJ, Gillette EL, McChesney AE. Use of radiotherapy for the treatment of intranasal tumors in cats: six cases (1980-1985). J Am Vet Med Assoc. 1986;189(8):927-9. Epub 1986/10/15. PubMed PMID: 3533873.
12. Meier VS, Beatrice L, Turek M, Poirier VJ, Cancedda S, Stiborova K, et al. Outcome and failure patterns of localized sinonasal lymphoma in cats treated with first-line single-modality radiation therapy: A retrospective study. Vet Comp Oncol. 2019. Epub 2019/06/30. doi: 10.1111/vco.12517. PubMed PMID: 31254440.
13. Mukaratirwa S, van der Linde-Sipman JS, Gruys E. Feline nasal and paranasal sinus tumours: clinicopathological study, histomorphological description and diagnostic immunohistochemistry of 123 cases. J Feline Med Surg. 2001;3(4):235-45. Epub 2002/02/14. doi: 10.1053/jfms.2001.0141. PubMed PMID: 11795961.
14. Sfiligoi G, Theon AP, Kent MS. Response of nineteen cats with nasal lymphoma to radiation therapy and chemotherapy. Vet Radiol Ultrasound. 2007;48(4):388-93. Epub 2007/08/19. PubMed PMID: 17691642.
15. Adams WM, Miller PE, Vail DM, Forrest LJ, MacEwen EG. An accelerated technique for irradiation of malignant canine nasal and paranasal sinus tumors. Vet Radiol Ultrasound. 1998;39(5):475-81. Epub 1998/10/15. doi: 10.1111/j.1740-8261.1998.tb01637.x. PubMed PMID: 9771602.

16. Lawrence JA, Forrest LJ, Turek MM, Miller PE, Mackie TR, Jaradat HA, et al. Proof of principle of ocular sparing in dogs with sinonasal tumors treated with intensity-modulated radiation therapy. Vet Radiol Ultrasound. 2010;51(5):561-70. Epub 2010/10/27. doi: 10.1111/j.1740-8261.2010.01695.x. PubMed PMID: 20973393; PubMed Central PMCID: PMCPMC2966034.
17. Soukup A, Meier V, Pot S, Voelter K, Rohrer Bley C. A prospective pilot study on early toxicity from a simultaneously integrated boost technique for canine sinonasal tumours using image-guided intensity-modulated radiation therapy. Vet Comp Oncol. 2018;16(4):441-9. Epub 2018/05/16. doi: 10.1111/vco.12399. PubMed PMID: 29761663.
18. Adams WM, Kleiter MM, Thrall DE, Klauer JM, Forrest LJ, La Due TA, et al. Prognostic significance of tumor histology and computed tomographic staging for radiation treatment response of canine nasal tumors. Vet Radiol Ultrasound. 2009;50(3):330-5. Epub 2009/06/11. PubMed PMID: 19507402.
19. McCoard SA, Fahrenkrug SC, Alexander LJ, Freking BA, Rohrer GA, Wise TH, et al. An integrated comparative map of the porcine X chromosome. Anim Genet. 2002;33(3):178-85. Epub 2002/05/29. PubMed PMID: 12030920.
20. Ladue T, Klein MK, Veterinary Radiation Therapy Oncology G. Toxicity criteria of the veterinary radiation therapy oncology group. Vet Radiol Ultrasound. 2001;42(5):475-6. PubMed PMID: 11678573.
21. Henderson SM, Bradley K, Day MJ, Tasker S, Caney SM, Hotston Moore A, et al. Investigation of nasal disease in the cat--a retrospective study of 77 cases. J Feline Med Surg. 2004;6(4):245-57. Epub 2004/07/22. doi: 10.1016/j.jfms.2003.08.005. PubMed PMID: 15265480.
22. Reed N. Chronic rhinitis in the cat. Vet Clin North Am Small Anim Pract. 2014;44(1):33-50. Epub 2013/11/26. doi: 10.1016/j.cvsm.2013.08.004. PubMed PMID: 24268332.
23. Michiels L, Day MJ, Snaps F, Hansen P, Clercx C. A retrospective study of non-specific rhinitis in 22 cats and the value of nasal cytology and histopathology. J Feline Med Surg. 2003;5(5):279-85. Epub 2003/09/02. doi: 10.1016/S1098-612X(03)00044-5. PubMed PMID: 12948503.
24. Adams WM, Bjorling DE, McAnulty JE, Green EM, Forrest LJ, Vail DM. Outcome of accelerated radiotherapy alone or accelerated radiotherapy followed by exenteration of the nasal cavity in dogs with intranasal neoplasia: 53 cases (1990-2002). J Am Vet Med Assoc. 2005;227(6):936-41. Epub 2005/09/30. PubMed PMID: 16190593.
25. LaDue TA, Dodge R, Page RL, Price GS, Hauck ML, Thrall DE. Factors influencing survival after radiotherapy of nasal tumors in 130 dogs. Vet Radiol Ultrasound. 1999;40(3):312-7. Epub 1999/10/16. PubMed PMID: 10519313.
26. Rassnick KM, Goldkamp CE, Erb HN, Scrivani PV, Njaa BL, Gieger TL, et al. Evaluation of factors associated with survival in dogs with untreated nasal carcinomas: 139 cases (1993-2003). J Am Vet Med Assoc. 2006;229(3):401-6. Epub 2006/08/03. doi: 10.2460/javma.229.3.401. PubMed PMID: 16881833.
27. Keyerleber MA, McEntee MC, Farrelly J, Podgorsak M. Completeness of reporting of radiation therapy planning, dose, and delivery in veterinary radiation oncology manuscripts from 2005 to 2010. Vet Radiol Ultrasound. 2012;53(2):221-30. Epub 2011/11/19. doi: 10.1111/j.1740-8261.2011.01882.x. PubMed PMID: 22092592.

Figure 1.

Kaplan-Meier plot showing the proportion of the 27 cats with sinonasal carcinoma alive: median overall survival 452 days (95%CI: 334;571). The vertical dashed lines represent the time points of 1 and 2 years, with 57% (95%CI: 37%;77%) and 27% (95%CI: 25%;29%) of cats alive, respectively. The small vertical lines represent censored cases.

Figure 2.

Kaplan-Meier plot showing time to progression for all 27 cats with sinonasal carcinoma after radiotherapy: median 269 days (95% CI: 225;314). The vertical dashed lines represent the time points of 1 and 2 years, with 24% (95%CI: 22%;26%) and 5% (95%CI: 5%;6%) of cats free of progression, respectively. The small vertical lines represent censored cases.

Figure 3

Kaplan-Meier plot showing the differences in survival for those cats with (red line) and without epistaxis (blue line). The median OS for cats with epistaxis was 828 days (95%CI: 356;1301) vs. 296 days (95%CI: 85;508) in cats without epistaxis, (p=.04, Breslow).

Table 1

Target volumes: mean volumes and absorbed doses (n=27)

Table 2 (supplementary data)

Patients characteristics.

Table 1

Target volumes: mean volumes and absorbed doses (n=27)

	Mean Volume (mean ± SD) [cm^3]	D_{max} (mean ± SD) [Gy]	D_{mean} (mean ± SD) [Gy]	D_{min} (mean ± SD) [Gy]
GTV	10.5 ± 9.2	45.0 ± 1.7	42.7 ± 0.5	39.3 ± 2.8
CTV	21.6 ± 13.2	45.6 ± 1.9	42.7 ± 0.5	37.6 ± 3.5
PTV	34.6 ± 18.7	45.8 ± 1.8	42.4 ± 0.5	32.5 ± 5.0